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EXAMINER	
FERNANDEZ, SUSAN EMILY	
ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/801,623	YUAN ET AL.	
	Examiner	Art Unit	
	Susan E. Fernandez	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-21 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-21 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/27/04, 3/21/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-21 are pending and are presented for examination.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-21 of this application.

Claim 1 recites that the method is "without chromatographic separation", which is not disclosed in provisional application 60/486,865. Moreover, claim 1 recites the limitation, "assessing the Hcy co-substrate conversion product SAH generated in step (a)", which is also not disclosed in the provisional application. Additionally, claims 8, 11, and 13 are not disclosed in the provisional application. Similarly, claim 14 also recites "assessing the Hcy co-substrate conversion product SAH...", where assessment is "without chromatographic separation". The provisional application fails to provide adequate support for the limitations recited in claims 15 and 17. Parent claims 18 and 21 recite a kits comprising "S-adenosylmethionine (SAM) or ATP, Met and a SAM synthase", and a "reagent for assessing adenosine (Ado)" or a "reagent for assessing SAH", which are not in the kit disclosed in 60/486,865 (page 7, paragraph [0031]). Additionally, claim 21 recites that the kit "does not comprise an enzyme or a reagent for generating H_2O_2 and a reagent for detecting H_2O_2" which is not a requirement in 60/486,865. Finally, claims 19 and 20 are not disclosed in the provisional application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered indefinite by the phrases "**assessing** the Hcy co-substrate conversion product SAH..." and "...adenosine (Ado), which is **assessed** to determine the presence, absence and/or amount..." First, it is not clear what features of SAH and Ado are assessed. The claim is confusing since no indication is given as to how the assessment of SAH relates to assaying homocysteine (Hcy), since the claim states that Ado is assessed to determine the presence, absence and/or amount of Hcy in the sample. Additionally, it is not clear what qualities of the assessed Ado feature would indicate the presence, absence and/or amount of the Hcy in the sample, as no criteria is given.

Claim 1 is also indefinite because it recites "...contacting the SAH with a SAH hydrolase to generate Hcy from **SAM**...", whereas the specification discloses that SAH hydrolase "catalyzes hydrolysis of SAH to adenosine (Ado) and Hcy" (page 10, paragraph [0041]). See also Figure 2. For examination purposes, the phrase will be read as "...contacting the SAH with a SAH hydrolase to generate Hcy from **SAH**..." Additionally, it is not clear whether Hcy or SAM (replaced with SAH for examination purposes) is cycled into the Hcy conversion reaction. Thus, claims 1-13 are rejected under 35 U.S.C. 112, second paragraph.

Claim 2 is indefinite because it is not clear what role the recited step has in assessing the Ado or in accomplishing the method for assaying Hcy. Thus, claims 2-5 are rejected under 35 U.S.C. 112, second paragraph.

Claim 3 is indefinite because it is not clear what features of Ado, the co-substrate, or the reaction product, are assessed. Furthermore, no criteria is given as to how the assessment of the Ado is effected by the assessment of the co-substrate or the reaction product. Thus, claims 3-5 are rejected under 35 U.S.C. 112, second paragraph. Claim 9 is rendered indefinite by the term, "the blood sample", since it lacks antecedent basis. The term is not recited in parent claims 1, 6, and 8. Thus, claim 9 is rejected under 35 U.S.C. 112, second paragraph.

Claim 14 is rendered indefinite by the phrase "**assessing** the Hcy co-substrate conversion product SAH...", as it is unclear what feature of SAH is assessed. No criteria is given as to what characteristics of the assessed feature would indicate the presence, absence and/or amount of the Hcy in the sample. Thus, claims 14-17 are rejected under 35 U.S.C. 112, second paragraph.

Claims 18 and 21 are rendered indefinite by the phrase "S-adenosylmethionine (SAM) or ATP, Met and a SAM synthase". As it is written it could be interpreted as one of the following: (i) (SAM or ATP) and Met and a SAM synthase, (ii) SAM or (ATP and Met and a SAM synthase). In view of claims 12, 13, 16, and 17, the phrase will be interpreted as option (ii). Additionally, claims 18 and 21 are indefinite because it is not clear what is defined by "a reagent for assessing" adenosine (Ado) or SAH. It is unclear what feature of Ado or SAH is assessed, thus it is unclear what reagents accomplish the assessment. Thus, claims 18-21 are rejected under 35 U.S.C. 112, second paragraph.

Claim 20 is rendered indefinite by the term,"the adenosine converting enzyme", since it lacks antecedent basis. The term is not recited in parent claims 1 and 18. Thus, claim 20 is rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-16 and 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuyama et al. (US 2002/0123088 A1) in view of Sundrehagen (US 5,958,717).

Matsuyama et al. teaches a method for determining the presence, absence, and/or amount of homocysteine (Hcy) in a sample wherein Hcy is first reduced, then reacted with a homocysteine-converting enzyme and a homocysteine co-substrate. See the abstract and claims

1, 4, and 5. Samples that may be tested with the method include biological samples such as body fluids (blood and urine) (page 1, paragraph [0010]).

The homocysteine-converting enzyme required for the method may be a methyltransferase, such as homocysteine methyltransferase [EC 2.1.1.10] (page 6, paragraph [0090]), which is also known as S-adenosylmethionine (SAM)-dependent homocysteine S-methyltransferase or S-adenosyl-L-methionine: L-homocysteine S-methyltransferase. When homocysteine methyltransferase is used, the enzyme produces L-methionine (Met) and S-adenosyl-L-homocysteine (SAH), where Hcy and SAM serve as the substrates. Note that Matsuyama et al. teaches a kit comprising SAM-dependent homocysteine S-methyltransferase and SAM, since the enzyme and substrate are together in a solution.

Matsuyama et al. indicates that "in all cases, L-methionine is produced, so that the amount of the homocysteine can be quantitatively determined by determining the L-methionine" (page 6, paragraph [0091]). However, because of the substantial presence of L-methionine in biological samples, D-methionine is detected and determined instead (page 6, paragraph [0092]).

Finally, Matsuyama et al. describes a method for determining homocysteine where SAH hydrolase is added to a sample in order to produce SAH, followed by reaction of the sample with adenosine deaminase (page 8, paragraph [0118]).

Matsuyama et al. does not expressly disclose assessing the produced SAH of the above reaction (catalyzed by SAM-dependent homocysteine S-methyltransferase) in order to determine the presence, absence and/or amount of Hcy in a sample (page 8, paragraph [0117]).

Sundrehagen discloses a method for assaying Hcy in a sample without chromatographic separation wherein the sample is contacted with SAH hydrolase, followed by the step of

"assessing (preferably photometrically) a non-labelled analyte selected from the homocysteine co-substrate and the products of the enzymic conversion of homocysteine by said enzyme" (column 2, lines 21-31). The reaction catalyzed by SAH hydrolase is given (column 3, lines 1-6), and it is noted that "in the preferred assay method of the invention, the SAH-hydrolase reaction may be used in either direction" (column 3, lines 37-38). According to claim 3, when SAH hydrolase is used, the analyte that is assessed is SAH. Assessment occurs by assessing adenosine (Ado). For appropriate analysis, detectable products are formed when adenosine is reacted with adenosine deaminase or adenosine kinase (column 4, lines 46-51). Additionally, Sundrehagen teaches a kit for performing the method that comprises SAH hydrolase and an adenosine converting enzyme, such as adenosine kinase (column 13, lines 9-11 and 16). SAH hydrolase is a reagent for assessing SAH. Finally, it is noted that the method can be applied to samples derived from "any biological fluid or tissue extract" (column 4, lines 9-12), including plasma or urine samples.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have modified the Matsuyama invention such that the presence of SAH is assessed instead of Met, by using the methods disclosed in Matsuyama et al. and Sundrehagen. The resulting reaction solution would have formed a kit comprising SAM-dependent homocysteine S-methyltransferase, SAM, SAH hydrolase, and an adenosine converting enzyme.

One of ordinary skill in the art would have been motivated to do this since Matsuyama et al. notes that L-methionine is generally present in biological samples prior to the Hcy assay (page 6, paragraph [0092]). To circumvent this problem, Matsuyama et al. offers a method to detect D-methionine for assaying Hcy. However, it would not have been possible to use that

method when SAM-dependent homocysteine S-methyltransferase is the methyltransferase. Thus, it would have been obvious to have detected SAH instead using the method disclosed by Matsuyama et al. and Sundrehagen. There would have been a reasonable expectation of success in using SAH assessment (through Ado assessment) following reaction of the sample with SAM-dependent homocysteine S-methyltransferase. A holding of obviousness is clearly required.

Claims 1-8, 10-12, 14-16, and 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuyama et al. and Sundrehagen as applied to claims 14-16 and 18-21 above, and further in view of Suzuki et al. (US 4,981,801) or Kawasaki et al. (US 2003/0138872 A1).

As discussed above, Matsuyama et al. and Sundrehagen render claims 14-16 and 18-21 obvious.

These references do not expressly disclose cycling the Hcy generated from the reaction catalyzed by SAH hydrolase into the Hcy conversion reaction by the SAM-dependent homocysteine S-methyltransferase.

Suzuki et al. discloses that enzymatic cycling permits the analysis of a very small amount of a substance in a sample. Moreover, "in the enzymatic cycling method, a substance is measured in a multiplying manner by combining two enzyme reactions." See column 1, line 63 through column 2, line 2.

Kawasaki et al. discloses a method involving enzymatic cycling for assessing the amount of homocysteine in solutions such as blood and urine (abstract). Specifically, "in an enzymatic cycling assay two or more enzyme activities are used which recycle substrate and do not

irreversibly convert the measured compound...instead the 'compound' is used catalytically to control the rate of conversion to the quantitated compound in the assay" (column 1, line 64 through column 2, line 3). Reaction rates are measured in the assay in order to determine the amount of analyte in the sample. Additionally, enzymatic cycling assays "typically increase the sensitivity of measurement for an analyte by 100- to 1000 fold" (column 2, lines 8-11). The enzymatic cycling assay taught by Kawasaki involves converting homocysteine to cystathionine by the enzyme CBS, and converting cystathionine to homocysteine by enzyme CBL, thus resulting in a steady state concentration of homocysteine (column 2, lines 28-33). The amount of homocysteine is determined based on the amount of conversion products or co-substrates detected (column 2, lines 36-39).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have cycled the Hcy formed from SAH back into the reaction catalyzed by SAM-dependent homocysteine S-methyltransferase.

One of ordinary skill in the art would have been motivated to do this in order to have enhanced the sensitivity of the assay, thus permitting measurements of miniscule amounts of Hcy. Moreover, the cycling would have been an expected occurrence since SAM-dependent homocysteine S-methyltransferase would not have been removed from the sample, thus resulting in its repeated use in further catalysis. A holding of obviousness is clearly required.

Claims 1-12, 14-16, and 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuyama et al., Sundrehagen, and Suzuki et al. or Kawasaki et al. as applied to claims 1-8, 10-12, 14-16, and 18-21 above, and further in view of Yuan (US 6,376,210).

As discussed above, Matsuyama et al., Sundrehagen, and Suzuki et al. or Kawasaki et al. render claims 1-8, 10-12, 14-16, and 18-21 obvious.

These references do not expressly disclose an assay for Hcy in every body fluid sample listed in claim 7. Furthermore, they do not disclose that, when the body fluid sample is blood, the blood sample is further separated into a plasma or serum fraction.

Yuan discloses a method for assaying Hcy in a sample (claim 1). Claim 11 indicates that the sample may be a body fluid selected from a group consisting of every species listed in claim 7 of the application under examination. Additionally, if the sample is blood, it is "further separated into a plasma or serum fraction" (claim 13).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have tested for Hcy in every type of sample listed in Yuan. Furthermore, it would have been obvious to have separated a blood sample into a plasma or serum fraction.

One of ordinary skill in the art would have been motivated to do this since there would have been a reasonable expectation of success in substituting one assay for another in detecting Hcy in a sample. Sample types and sample processing disclosed in one Hcy assay would have been considered suitable for use in other Hcy assays. A holding of obviousness is clearly required.

Claims 1-8 and 10-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuyama et al., Sundrehagen, and Suzuki et al. or Kawasaki et al. as applied to claims 1-8, 10-12, 14-16, and 18-21 above, and further in view of Nelson et al. (Lehninger Principles of Biochemistry, 3rd edition, 2000, pages 640-642).

As discussed above, Matsuyama et al., Sundrehagen, and Suzuki et al. or Kawasaki et al. render claims 1-8, 10-12, 14-16, and 18-21 obvious.

These references do not expressly disclose producing SAM from ATP and Met by a SAM synthase.

Nelson et al. discloses that methionine adenosyl transferase, also known as S-adenosylmethionine synthase (SAM synthase) in the art, catalyzes the conversion of Met to SAM, where ATP is a co-substrate. See pages 640 and 642, particularly Figure 18-17.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have used the reaction described by Nelson et al. in order to produce SAM for the reaction catalyzed by SAM-dependent homocysteine S-methyltransferase.

One of ordinary skill in the art would have been motivated to do this since there would have been a reasonable expectation of success in producing SAM from Met and ATP by SAM synthase. Both Met and ATP would have been expected to have been present in most body fluids. A holding of obviousness is clearly required.

Claims 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yuan (U.S. Pat. 6,610,504) in view of Shapiro (Methods Enzymol. 1971. 17(Pt. B): 400-405).

Yuan discloses a method comprising the step of "contacting a SAM-dependent methyltransferase with a substrate of the methyltransferase in the presence of SAM..." resulting in the conversion of SAM into SAH (claim 1). Then, steps are taken to "detect or determine the presence or amount of the SAH".

Yuan does not expressly disclose that the substrate of the methyltransferase is Hcy, or that one of the products of the conversion is methionine (Met). Furthermore, Yuan does not correlate the detection of SAH to the detection of Hcy, or expressly disclose that SAM is added to the sample.

Shapiro discloses that reaction of homocysteine (Hcy) and adenosylmethionine (SAM) yields methionine (Met) and adenosylhomocysteine (SAH) when catalyzed by S-adenosylmethionine:homocysteine methyltransferase (SAM-dependent methyltransferase) (page 400). There is an equimolar relationship between the reactants and the products, as indicated by the reaction on page 400 and the second paragraph of page 405.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have used Hcy as the substrate of the methyltransferase of the Yuan invention in the presence of SAM, thus resulting in SAH and Met as products. Furthermore, it would have been obvious to have related the detection and amount of the SAH performed by Yuan to the detection and amount of Hcy in a sample tested by the Yuan invention.

One of ordinary skill in the art would have been motivated to do this in order to have introduced a new use to the Yuan invention, resulting in dual-purpose invention which would have enhanced efficiency. Additionally, one would have been motivated to have added SAM in order to have ensured that Hcy would not have been the rate-limiting substrate of the reaction, thus it would have confirmed that SAH detection correlates to Hcy detection. A holding of anticipation is clearly required.

Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yuan and Shapiro as applied to claims 14-16 above, and further in view of Nelson et al.

As discussed above, Yuan and Shapiro render claims 14-16 obvious.

Yuan and Shapiro do not expressly disclose that the SAM is produced from ATP and Met by a SAM synthase.

Nelson et al. discloses that methionine adenosyl transferase, also known as S-adenosylmethionine synthase (SAM synthase) in the art, catalyzes the conversion of Met to SAM, where ATP is a co-substrate. See pages 640 and 642, particularly Figure 18-17.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have used the reaction described by Nelson et al. in order to produce SAM for the Yuan invention.

One of ordinary skill in the art would have been motivated to do this since there would have been a reasonable expectation of success in producing SAM from Met and ATP by SAM synthase. Both Met and ATP would have been expected to have been present in most body fluids. A holding of obviousness is clearly required.

Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chagoya de Sanchez et al. (Int. J. Biochem. 1991. 23(12): 1439-1443) in view of Kuchino et al. (Cancer Research. 1977. 37: 206-208).

Chagoya et al. discloses that SAM, SAH hydrolase, adenosine kinase, and adenosine deaminase are present in rat liver (page 1440, Figures 1 and 2). Thus, the rat liver is a kit comprising SAM, SAH hydrolase, adenosine kinase, and adenosine deaminase.

Chagoya et al. does not expressly disclose a kit comprising SAM-dependent homocysteine S-methyltransferase.

Kuchino et al. discloses that S-adenosylmethionine homocysteine methyltransferase, also known as SAM-dependent homocysteine S-methyltransferase, is in rat liver, as its activity was detected (page 207, "Results"). Thus, the rat liver is a kit comprising SAM-dependent homocysteine S-methyltransferase.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have concluded that the rat liver would have served as a kit comprising SAM, SAH hydrolase, adenosine kinase, adenosine deaminase, and SAM-dependent homocysteine S-methyltransferase. Additionally, it would have been obvious to have assayed Hcy in a rat liver sample.

One of ordinary skill in the art would have been motivated to have reached this conclusion since there had been evidence that normal rat liver samples contained the enzymes and substrates listed above. Furthermore, detection and measurement of Hcy in a rat liver sample would have provided Kuchino et al. further information about SAM-dependent homocysteine S-methyltransferase activity. A holding of obviousness is clearly required.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan E. Fernandez whose telephone number is (571) 272-3444. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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sef

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PRIMARY EXAMINER